REMARKS

Interview request

Applicants respectfully request a telephonic interview after the Examiner has reviewed the instant response and amendment. Applicants request the Examiner call Applicants' representative at 858 720 5133.

Status of the Claims

Pending claims

Claims 1, 3 to 11 and 25 to 36 are pending and under consideration.

Claims added in the instant amendment

In the present response, claims 37 to 42 are added. Thus, after entry of the instant response, claims 1, 3 to 11 and 25 to 42 will be pending.

Outstanding Rejections

The rejection of claims 1, 3 to 11 and 25 under 35 U.S.C. §103, alleging these claims obvious over Morton, et al., WO 95/15338; hereinafter "Morton") in view of The Interferon Beta Multiple Sclerosis Study Group (Neurology, 1993, 43:655-661; hereinafter "the MS Study"), has been maintained. Claims 1, 3 to 11 and 25 to 36, are newly rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. Claims 8 to 11 are newly rejected under 35 U.S.C. § 112, first paragraph, written description requirement. Claims 6 and 30 are newly rejected under 35 U.S.C. § 112, first paragraph, enablement requirement.

Applicants respectfully traverse all outstanding objections to the specification and rejection of the claims.

Support for the claim amendments

The specification sets forth an extensive description of the invention in the new and amended claims. For example, support for methods of the invention wherein the IFN-β is administered at a dose that does not produce IFN-β–induced side effects in the individual, can be found, inter alia, on page 12, lines 10 to 13, of WO 00/43033 (the publication of the priority

document PCT/AU00/00032). Support for methods of the invention encompassing cpn10 and IFN-β combination therapy wherein cpn10 and IFN-β provide greater relief from disease symptoms than does IFN-β alone, thereby reducing the need for IFN-β to be administered at doses which produce side effects, can be found, inter alia, on page 13, lines 3 to 6, of WO 00/43033. Support for methods of the invention encompassing administration of cpm10 in the form of a tablet or a capsule, can be found, inter alia, on page 14, lines 13 to 14, of WO 00/43033.

Accordingly, Applicants respectfully submit that no new matter is introduced by the instant amendment.

Issues under 35 U.S.C. §103

The rejection of claims 1, 3 to 11 and 25 under 35 U.S.C. §103 has been maintained, for reasons of record. Applicants respectfully traverse for reasons set forth in Applicant's previous responses, including, inter alia, supporting data set forth in the specification and the submitted expert declaration by Dr. Johnson.

However, before addressing these issues in detail, Applicants wish to emphasize that the instant claimed invention can be characterized as three separate embodiments:

(I) Synergistic action: In one embodiment, the invention provides methods of treating MS comprising administering to an individual in need thereof a pharmaceutically-effective amount of both cpn10 and IFN-β, wherein the therapeutic effect of administering both cpn10 and IFN-β is improved (synergistic) as compared to the therapeutic effect of administering the same amount of cpn10 or IFN-β alone. See, e.g., independent claim 1.

(II) Suboptimal dosages: In a second embodiment, the invention provides methods of treating MS in an individual taken off IFN-β treatment or having reduced dose IFN-β treatment because of IFN-β-induced side effects, the method comprising the steps of administering to an individual in need thereof a combination treatment comprising pharmaceutically-effective amounts of both cpn10 and IFN-β, wherein the IFN-β is administered at a dose that does not produce

IFN-β–induced side effects in the individual. Synergistic action of cpn10 and IFN-β is not a limitation. See, e.g., independent claim 25.

(III) Delaying relapse of MS: In a third embodiment, the invention provides methods of delaying relapse to an active from an inactive state of MS, comprising (a) providing a pharmaceutical composition comprising both cpn10 and IFN-β, or providing two pharmaceutical compositions each comprising cpn10 or IFN-β, wherein one of the pharmaceutical compositions comprises cpn10 and the other pharmaceutical composition comprises IFN-β; and (b) administering to an individual in need thereof a pharmaceutically-effective amount of the cpn10 and IFN-β. See, e.g., independent claim 26.

Embodiments (I) and (II) are subject to the maintained section 103 rejection, while embodiment (III) is not; and addressing embodiments (I) and (II) in turn:

(I) Synergistic action:

Applicants respectfully traverse the Office's allegations that the arguments as set forth in Applicants' responses, the data set forth in the specification and the submitted expert declaration by Dr. Johnson do not support the synergistic action of cpn10 and IFN-β in treating MS seen when practicing this invention, e.g., by administering a pharmaceutically-effective amount of both cpn10 and IFN-β; Applicants reiterate and incorporate those arguments and responses herein.

The cited Morton describes the use of chaperonin 10 (cpn10) for the treatment of experimental allergic encephalomyelitis (EAE), an animal model for human MS. Morton does not teach or suggest administration of IFN-β. The MS Study describes use of IFN-β for the treatment of MS, but does not teach or suggest use of cpn10. Thus, neither reference teaches or suggests the combination of cpn10 and IFN-β for the treatment of MS.

While Applicants will not repeat all their previous arguments in this response, they do wish to emphasize Dr. Johnson's expert declaration (submitted with the response of October 27, 2005) that there was no motivation to combine the cited references (Morton in view of the MS study) because, inter alia, it was not possible to predict in advance the outcome of combining two

agents, and that this is particularly true with autoimmune diseases (Dr. Johnson is an expert in the field of clinical immunology) (see, e.g., page 2, paragraph 6, of her declaration); and is also particularly true because at the time of the invention it was thought (wrongly) that cpn10 and IFN-β acted against MS using similar immunosuppressive mechanisms (see page 3, paragraph 8, of her declaration).

Dr. Johnson further supports her expert opinion that there was no motivation to combine the two cited references with Jeffrey (2004) Neurology 63:S41-S46 (see, e.g., page 2, paragraph 7, of her declaration), who clearly expressed the opinion that "the agent added to the primary therapy may have no effect, or, worse, may antagonize the effect of the primary agent", as discussed in detail in the declaration. Thus, not only was there no motivation in the state of the art at the time of the invention, the art expressly warned against combinations: "the [second] agent ... may have no effect, or, worse, may antagonize the effect of the primary agent".

Also as explained by Dr. Johnson, the claimed invention is based, inter alia, on the discovery that because cpn10 and IFN-β act via different biological mechanisms they act co-operatively to reduce MS symptoms and decrease relapse frequency. However, as declared by Dr. Johnson, at the time of this invention the art clearly described cpn10 and IFN-β as acting via similar mechanisms – a scenario which is not predictive of synergism. Thus, as declared by Dr. Johnson, at the time of this invention a skilled artisan would not have been able to predict an improved (synergistic) therapeutic effect upon the combined administration of cpn10 and IFN-β. Accordingly, Applicants respectfully submit, inter alia, that because the state of the art at the time of the invention wrongly thought cpn10 and IFN-β acted via a common mechanism of action, and because the prior art implicitly taught away from the present invention ("the [second] agent ... may have no effect, or, worse, may antagonize the effect of the primary agent") there was no – or negative – motivation to combine Morton or the MS Study to teach the claimed invention. See paragraphs 6 to 13, pages 2 to 5, of the expert declaration. Thus, Applicants have specifically distinguished the invention (combination cpn10 and IFN-β therapy) with the teachings of Morton (cpn10 only) and the MS study (IFN-β only).

As noted above, the Office also alleged the data set forth in the specification and the submitted expert declaration by Dr. Johnson do not support the synergistic action of cpn10 and IFN-β in treating MS seen when practicing this invention, see, e.g., pages 4 and 5 of the OA. In response, Applicants reiterate and incorporate their previous arguments and Dr. Johnson's declaration herein. However, because the Office referenced claims 10, 11, 35, directed to specific dosages, alleging that they would not be considered "suboptimal" (see, e.g., page 5, lines 16 to 19, of the OA), Applicants wish clarify that synergy can occur when practicing the invention using either optimal or suboptimal dosages of cpn10 or IFN-β. This response also clarifies this issue - after entry of the instant amendment, claims directed to dosages (claims 8 to 11, 35) will only depend on claim 1, encompassing the synergistic action of cpn10 and IFN-β, not use of suboptimal dosages of cpn10 or IFN-β.

(II) Suboptimal dosages:

As noted above, in a second embodiment, the invention provides methods of treating MS in an individual taken off IFN-β treatment or having reduced dose IFN-β treatment because of IFN-β-induced side effects, the method comprising the steps of administering to an individual in need thereof a combination treatment comprising pharmaceutically-effective amounts of both cpn10 and IFN-β, wherein the IFN-β is administered at a dose that does not produce IFN-β–induced side effects in the individual. See, e.g., independent claim 25. Because neither Morton nor the MS study teach or suggest administering IFN-β in a combination therapy to allow the IFN-β to be administered at dosages which would be clinically ineffective if IFN-β were given alone, e.g., doses that does not produce IFN-β–induced side effects in the individual, neither cited reference alone or in combination teaches or suggests the claimed invention.

Accordingly, in view of Applicants remarks herein and their previous response submissions, including Dr. Johnson's declaration, and the instant amendment, the rejection under 35 U.S.C. §103(a) can be properly withdrawn.

Evidence of secondary indicia of nonobviousness rebuts a possible prima facie case

Finally, the Office alleges that Dr. Johnson's declaration was insufficient to support Applicants assertion that there was a long-felt need for an effective method for treating MS using IFN-β without inflicting its deleterious side effects on patients, a problem solved by one aspect of this invention. In their last response, to rebut any possible *prima facie* case of nonobviousness, Applicants submitted objection evidence of nonobviousness in the form of an expert declaration by Dr. Johnson that there was a long-felt need for an alternative MS treatment. Applicants respectfully averred that their submission of evidence of secondary indicia of nonobviousness overcame any possible obviousness rejection, even if, *arguendo*, the Patent Office showed sufficient evidence of *prima facie* obviousness.

Dr. Johnson declared that there was a long-felt need for a treatment such as that claimed in this application. She notes that throughout the 20th century scientists and physicians have sought effective treatments for MS with limited success (see Dr. Johnson's expert declaration, paragraph 4, page 1). Dr. Johnson declares that this invention offers a solution to this long felt need by providing an effective therapy using cpn10 and IFN-β together. Dr. Johnson also declares that it is worthy to note that in spite of years of intensive research by many investigators no one had, before the present invention, taught or suggested a therapy for MS comprising combined administration of beta-interferon and chaperonin 10 (see Dr. Johnson's expert declaration, paragraph 5, page 2).

The Office alleged that the declaration was insufficient because, inter alia, there was no evidence that if persons skilled in the art knew of the teaching of the cited art, they would still be *unable* to solve the problem (see, e.g., page 6, lines 18 to 21, the OA; emphasis added). Indeed, as declared by Dr. Johnson, in spite of the pressing need for an alternative MS treatment and years of intensive research by many investigators, in spite of the teachings of the cited references, no one had before this invention taught or suggested a therapy for MS comprising combined administration of beta-interferon and chaperonin 10.

Accordingly, in view of the above remarks and the evidence of secondary indicia of nonobviousness as set forth in the declaration of Dr. Johnson, Applicants submit that they have

rebutted any possible *prima facie* case of nonobviousness. Accordingly, the Examiner is respectfully requested to withdraw the rejection under 35 U.S.C. §103(a).

Issues under 35 U.S.C. §112, second paragraph

Claims 1, 3 to 11 and 25 to 36, are newly rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite, as set forth in detail in paragraph 8, pages 7 to 8, of the OA. The instant amendment addresses this issue.

In particular, in paragraph 8c of the OA (see page 8, lines 6 to 9), it is alleged that the phrase "clinically significant IFN-β-induced side effects in the individual" in independent claims 25 and 32, is vague in that it is not defined in the specification. Applicants note that these claims are amended to read on methods wherein the IFN-β is administered at a dose that does not produce IFN-β–induced side effects in the individual, as expressly supported by the specification on page 13, lines 3 to 6, of WO 00/43033. It was well known in the art at the time of the invention that IFN-β administration at certain dosages could produce side-effects, and it was well known what those side effects were. What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail in the specification. See Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d at 1384, 231 USPQ at 94. If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met. See, e.g., Vas-Cath, 935 F.2d at 1563, 19 USPQ2d at 1116; Martin v. Johnson, 454 F.2d 746, 751, 172 USPQ 391, 395 (CCPA 1972) (stating "the description need not be in *ipsis verbis* [i.e., "in the same words"] to be sufficient"). MPEP 2163 II.A.3.(a), page 2100-180, 8th ed., Rev. 3, Aug. 2005.

Rejections under 35 U.S.C. §112, first paragraph - written description

Claims 8 to 11 are newly rejected under 35 U.S.C. § 112, first paragraph, written description requirement, as set forth in detail in paragraph 9, pages 8 to 9, of the OA. The instant amendment addresses this issue. Accordingly, the rejection under section 112, written description requirement, can be properly withdrawn.

Rejections under 35 U.S.C. §112, first paragraph- enablement

Claims 6 and 30 are newly rejected under 35 U.S.C. § 112, first paragraph, enablement requirement, as set forth in detail in paragraph 10, pages 9 to 10, of the OA. The instant amendment addresses this issue.

The Office noted that the specification is enabling for administration of cpn10 and IFN-β for the treatment of MS in liquid or solution form.

However, it is alleged that the specification does not provide reasonable enablement for treating MS by administering cpn10 and IFN-β using tablet or capsule form. The instant amendment addresses this issue. As expressly set forth, inter alia, on page 14, lines 13 to 14, of WO 00/43033, after entry of the instant amendment, claim 6 and 30 are directed to administration of cpm10 in the form of a tablet or a capsule. Methods for making and using tablets and capsules incorporating compositions similar to cpn10 were well known in the art at the time of the invention. Accordingly, the rejection under section 112, enablement requirement, can be properly withdrawn.

CONCLUSION

In view of the foregoing amendment and remarks, Applicants respectfully aver that the Examiner can properly withdraw the rejection of the pending claims under 35 U.S.C. §112, first and second paragraphs, and 35 U.S.C. §103(a). In view of the above, claims in this application after entry of the instant amendment are believed to be in condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejections of the claims and to pass this application to issue.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 284502000600. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

As noted above, Applicants have requested a telephone conference with the undersigned representative to expedite prosecution of this application. After the Examiner has reviewed the instant response and amendment, please telephone the undersigned at (858) 720-5133.

Dated: March 29, 2006

Respectfully submitted,

By

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